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A prospective study on disorders of sex development in Duhok city, Kurdistan region, Iraq: Genetic, etiology and clinical presentation

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ABSTRACT

Disorders of Sexual Development (DSD) encompass all types of intersex cases and have been reported globally. However, in Iraq, studies related to DSD are scanty. The current single-center prospective study was carried out to find out the frequency, genetic and clinical presentation of different types of DSDs in the sample population of Duhok, Iraq. The sample comprises 40 DSD patients who have been referred to Hivi Pediatric Teaching Hospital in Duhok, Kurdistan region, Iraq, from June 2017 to June 2022. We conducted karyotype-based classification, laparoscopic-based internal organ diagnosis and abdominal ultrasound to diagnose DSDs in the target population. Of the total 40 cases, 19 (47.5%) were males, and 21 (52.5%) were females. Among them, 85 % were diagnosed as peno- scrotal hypospadias, 10% had clitoromegaly and the remaining were diagnosed as under-developed female-like genitalia. The majority of the patients were diagnosed with congenital adrenal hyperplasia (CAH) (55%), 37.5% were Testicular Feminization Syndrome (TFS) and the remaining were rare categories that we did not reach final diagnosis. Laparoscopy was done for 77.5 % of the participants of whom 30% had small uterus and ovaries, 25% had Intra-abdominal testes and the remaining had testes &ovaries, Mullerian Inhibitory Factor (MIF) deficiency and TFS. The study found different types of DSDs in the target population that requires both physical and psychological intervention. Future studies should focus on evaluating DSDs in larger populations and at multi-centers to understand the condition's trajectory in the Iraqi population.

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Introduction

A set of congenital problems pertaining to the unusual development of internal and external genital formations are referred to as disorders of sexual development (DSD) (1). Variances in developmental programming, genes, and hormones have been reported as causal factors of such conditions (2). The ambiguous nature of external genitalia helps in the easy recognition of such patients at birth. Some individuals might exhibit postnatal masculinization, stalled or nonexistent puberty, or fertility problems eventually. Global stakeholders from a multitude of fields keep changing the terms applied to classify particular DSDs in order to highlight the fundamental genetic factors (3). The recurring research and implementation of potential molecular cytogenetic methodologies have augmented comprehension of the chromosomal abnormalities connected to DSDs. Furthermore, studies of such genetic mutations have revealed novel genetic control mechanisms linked to DSDs (4).

Unusual decision-making difficulties may arise concerning a child who has atypical genitalia in terms of the sex of raising, parenting, patient training, and treatment approaches (5). It is crucial to understand that sex indicates the biology of the inner and outer genital formations, which is generally viewed as a binary classification rather than gender. The way a person experiences their gender is known as their gender identity. The transitions and spontaneity in sex and gender identity have been evidenced and commemorated in stories from Greco-Roman civilizations, such as Hermaphrodite and Daphne (6).

When the gonad renounces its bipotential condition due to the impact of the sex-determining genes, phenotypic sex results from the differences between inner ducts and outer genitals under the action of the distinctive gonad's hormones (7). The Chicago Consensus, 2006 characterized disorders of sexual development (DSD) as a condition where gonadal, chromosomal, and anatomical sex development is unusual (8). Potential benefits of the terminology include its precision in a medical sense and its avoidance of ambiguity by avoiding similarity with terms like gender dysphoria, transgender, and homosexuality. Nevertheless, patients' perceptions of DSD's social stigma include the prejudices of "disorder" and the notion that "sex" implies engaging in sexual activity (9). Since the traits are related or nearly identical and can have various aetiologies, clinical categorization in patients is challenging (10). There is uncertainty regarding the prevalence of the conditions mentioned because the term is not defined clearly. When taking into account all genital congenital complications, such as cryptorchidism and hypospadias, the occurrence could range from 1:200 to 1:300 (11). Its independent occurrence is thought to be 1 in 4,500–5,500 neonates (6). The global burden of DSD in 46, XX individuals (primarily congenital adrenal hyperplasia) is projected to occur in 14,000–15,000 babies born (12). This

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occurrence differs from place to place because of variations in the recurrence of genetic variations. One-half of all DSD patients who diagnostically display genital ambivalence have mixed gonadal dysgenesis and congenital adrenal hyperplasia (13). In addition to being diagnosed at a later age in people with delayed puberty, unpredicted virilization or gynecomastia, infertility, or gonadal tumors, such situations may additionally be detected in foetuses or neonatal with unclear external genitalia, gonadal dysgenesis, and internal genitalia which are dissonant for such condition of sex chromosomes. It is possible that DSD will, every once in a while, be a component of a genetic disorder, highlighting the intricacies of sexual development and the influence of many genes.

In past years, DSD studies have concentrated on finding genetic variations that cause the unusual advancement of sex using various methods. Nevertheless, nearly 50% of the time, it found a causative link (14). The lack of understanding of the pathogenesis and mechanisms underlying DSD, variations in assessment and phenotypic explanation, and a lack of comprehension of the significance of molecular and genetic prognosis to inform treatment and management of the entity is probable to be the causes of this diagnosis disparity (15).

Medical treatment for DSDs is noted for the problems pertaining to unusual genitalia, such as congenital adrenal hyperplasia (CAH), and is dependent on the root cause. If the gonadal function fails, additional hormone treatment may be used (16).

Regarding the surgical management of DSDs, there is still a great deal of debate. Gender reassignment problems are at the center of the debate. Gender assessment by the health care professional and family don't always correspond with individual sexual preference.

A ban on gender reassignment and genital surgical intervention has been requested by a number of activists and medical practitioners (17).

In the context of Iraq, there is no definitive data on disorders of sex development. One research in 2019, in their review, described only disorders of sexual development, types, aetiologies, and mechanism. No discussion was on the prevalence or incidence rate of DSD in Iraq. Similarly, other studies have carried out reviews on DSDs, types, presentation variations, and aetiologies. To our knowledge, most research studies in Iraq are based on sexual dysfunction in males and females and their biological study. Ours is the first study in Duhok City that evaluates DSDs in a sample of 40 patients. The study findings will help clinicians, clinical psychiatrists, psychologists, and other healthcare professionals to help people suffering from DSDs. (12)

Materials and Methods

Recruitment of patients

Forty patients diagnosed with DSD presented to Hivi Pediatric Hospital in Duhok, Iraq's Kurdistan area, between June 2017 and June 2022 were considered for the current study.

Ethical clearance

The local directorate of health's Health Ethics Committee provided ethical clearance for the study. All of the patient's diagnoses and treatments were made using clinical characteristics and image analysis results. Additionally, the chromosomal analysis was carried out to validate the prognosis. The ethical clearance number for the current study is 18052022-3-9.

Methods

Each patient's clinical characteristics were identified to organize them according to their phenotype. AMF (anti mullerian factor) and gonadotrophin concentration were also measured, along with 17-hydroxyprogesterone, a cytogenetic analysis (karyotype), blood electrolytes, and an abdomen ultrasound to look for Müllerian structures. Laparoscopy had been performed for additional diagnostic tests and follow-up for certain respondents.

The 17-OH-Progesterone was determined by 17-OH Progesterone (Cat. No.: HYD-5333). The serum was collected from the 5 ml aspirated blood that was allowed to clot. The clotted blood was subjected to centrifugation for obtaining serum. The enzyme-linked immunosorbent assay (ELISA) test was used to determine the 17-OH-Progesterone level. The follicle-stimulating hormone (FSH) and Leutinizing hormone (LH) both were determined through Electro-chemiluminescence immunoassay (ECLIA). The assay kit is Elecsys FSH (Cat. No.: 11775863), and the assay was run in Cobas e411 (Roche/Germany). To separate serum from the blood, the same procedure was followed as 17-OH-Prgesterone determination. For karyotyping, the G-Banding method was used. The electrolyte testing was carried out by Ion-Selective Electrode (ISE) and cobas c311 (Roche/Germany) was used by obtaining serum from blood as previously mentioned. The karyotyping was observed through a Zeiss microscope with Ikaros karyotyping software (MetaSystems company/Germany). The ultrasound (U/S) was done by Using SIEMENS ACUSON S1000 and at frequencies 9l4 megahertz, and 6C2 megahertz. The diagnostic laparoscopy used for evaluating pelvic organs used TEKNO laparoscopy tower instruments by umbilical cord port 5mm, 2 ports at right and left iliac fossa 3 mm under Co2 pressure 12 mmHg.

Statistical analysis

Microsoft Excel was used to enter the data and data cleaning. Further analysis was carried out by exporting data to SPSS version 21 was then used to evaluate. In order to determine the mean, frequency (%), and standard deviations, descriptive statistical analysis was used. Classification variables have been shown as frequency (%) and continuous variables as mean$\pm$SD with maximum and minimum values. P values less than 0.05 were considered to be statistically significant.

Results

A total of 40 DSD patients were included in the study. The patients were studied for demographic characteristics, phenotype and clinical characteristics, genetic analysis, final diagnosis, and laparoscopic findings. The study included male and female patients with ages ranging from 0.3-5.6 years (Table 1). Patients with ages ranging from 3-5 years had the highest percentage (62.5%) of DSD diagnosis, followed by 1-3 years and then less than 1 year. The study showed that among 40 cases, 19 (47.5%) were males, and 21 (52.5%) were females (Table 2).

Among these, 2 patients had a family history of DSD,

and 8 patients had a history of consanguineous marriage.

Phenotypical and clinical analysis showed 85 % presented with ambiguous genitalia, thus diagnosed as penoscrotal hypospadias, 10% of patients had large clitoris indicating clitoromegaly, and the remaining patients (5%) were diagnosed as under-developed female-like genitalia (Table 3).

Karyotyping revealed that 20 (50%) patients had the XY genotype, 19 (47.5%) patients had the XX genotype, and 1(2.5%) patient had the XO genotype indicating Turner Syndrome (Table 4).

All the initial studies applying First-line tests like measurement of 17-hydroxyprogesterone, blood electrolytes, determination of AMF and gonadotrophin levels, cytogenetic study (karyotype), and abdominal ultrasound in search of müllerian structures led to the final diagnosis which showed that majority of the patients were diagnosed with CAH (55%), followed by 37.5% with Testicular Feminization Syndrome and remaining with rare categories that remained unconcluded for final diagnosis (Table 5).

Table 1. Age-wise distribution of the study population.

Age	No. (%)
Less than 1 year	6 (15)
1 to 3 years	9 (22.5)
3 to 5 years	25 (62.5)
Total	40 (100)

Table 2. Gender distribution of the study population.

Gender	No. (%)
Male	19 (47.5)
Female	21 (52.5)
Total	40 (100)

Table 3. Phenotypes and clinical characteristics of the study participants.

Phenotype	No. (%)
Ambiguous	34 (85)
large clitoris	4 (10)
under developed females like	2 (5)
Total	40 (100)

Table 4. The results of the Genetic analysis of the participants with disorders of sexual development.

Genotype	No. (%)
XY	20 (50)
XX	19 (47.5)
XO	1 (2.5)
Total	40 (100)

Table 5. Final diagnosis of the diseases that caused the disorders of sexual development in the study population.

Diagnosis	No. (%)
CAH	22 (55)
Testicular Feminization Syndrome	15 (37.5)
Turner	1 (2.5)
Others	2 (5)
Total	40 (100)

Table 6. Laparoscopic findings of the internal genital organs among the participants of the study.

diagnosis Laparoscopy	No. (%)
Both the testis & ovaries	6 (15)
Intra-abdominal testis	10 (25)
small uterus and ovaries	12 (30)
Mullerian inhibiting factor deficiency	1 (2.5)
not done	9 (22.5)
TFS	2 (5)
Total	40 (100)

Additional diagnostic laparoscopy in 31 patients out of 40 (77.5%) revealed that the majority of the patients presented small uterus and ovaries (30%), 25% had Intra-abdominal testis, and the remaining had both testis and ovaries and TFS (Table 6).

Discussion

Disorders of sex development (DSDs) are a broad category of clinical conditions in which the chromosomal, autosomal sex and gonadal is abnormal. Because this cluster of disorders is so diverse, identifying a genetic prognosis can be difficult. A variation in the genes, a variance in how individuals react to sex hormones within the body, or both are the leading causes of DSD (18). Although it can be inherited, there is frequently no obvious cause. When an individual is a teenager or close to their birth, it is most typical to learn that they have a DSD. Sex chromosome disorders, 46, XY abnormalities of testis development and androgenization, and disorders of ovary development and androgen abundance are all examples of DSD (46, XX DSD) (19). Different DSD contributing factors have different clinical indications, which are reflected in the variability of DSD phenotypes. DSD affects one in every 4500 to five thousand live births. The decision-making process regarding sex assessment has been viewed by families and medical practitioners as being deeply upsetting and challenging, constituting a social emergency (20). A cooperative approach by a team consisting of an endocrinologist, a paediatrician, a surgeon, a radiologist, and a lab technician is necessary for the care of patients with DSD. Exterior genitalia virilization at birth is reliant on intrauterine exposure to androgens, which can come from testicles, adrenal glands, or occasionally exogenous sources (21). Mullerian structures generally indicate a genetic male sex or gonadal dysgenesis in a genetic male with insufficient anti-Mullerian hormone production (AMH). The sex of rearing is determined by genetic sex, the level of virilization of the external genitalia, the likelihood of regaining fertility and the presence of the external genitalia, as well as parental and patient choices. Although genital surgery is frequently necessary, there is still controversy over the procedure's type and timing (22).

The purpose of this study is to assess the incidence of sex development disorders (DSD) in the city of Duhok (referred to as Hivi Paediatric Teaching Hospital). Additionally, we aimed at investigating the clinical profile and management of patients with sex development disorders. The current study included a total of 40 DSD patients who were connected to the Hivi Pediatric Hospital in Duhok, Iraq's Kurdistan region, between June 2017 and June 2022.

The patients' phenotype, demographic analysis, genetic analysis, final diagnosis, and laparoscopic findings were all analysed.

Participants in the demographic study were both male and female patients, ranging in age from 0.3 to 5.6 years. The majority (62.5%) of patients with a diagnosis of DSD were between the ages of 3-5 years, followed by 1-3 years and less than 1 year. According to the study, out of 40 cases, 19 (47.5%) of cases involved males and 21 (52.5%) involved females. There are similar reports of DSDs where children diagnosed with DSD were more likely to be assigned the female gender at birth (23).

Various studies have reported the correlation of DSDs with consanguinity in several countries (24-27). Similarly, in our study, we found that two patients had a DSD family history, and eight had a background of consanguineous marriage.

Infants with unclear or abnormal genitalia may have phenotypic sex that is not clear. All of the patients' diagnoses were made using clinical characteristics and imaging results. Additionally, a chromosomal study was carried out to validate the diagnosis. The clinical characteristics for each patient were identified in order to group them according to their phenotype. Phenotypical and clinical analysis revealed that 85% of patients had ambiguous genitalia, which led to the diagnosis of penoscrotal hypospadias, 10% had large clitoris, which indicated clitoromegaly, and the remaining patients (5%), who had underdeveloped genitalia that resembled those of a female. Micro penis, undescended/impalpable testis and scrotal anomaly are all symptoms of DSD (28). The opening in the penoscrotal hypospadias is positioned where the shaft meets the scrotum (29). Clitoromegally is caused by a small number of clinical entities. The 46XX DSD condition congenital adrenal hyperplasia is the most frequent cause of clitoris enlargement (CAH) (30).

The broadly used, gold-standard technique for detecting chromosomal abnormalities bigger than 5–10 Mb is traditional G–banded karyotyping. Karyotyping, which assesses chromosomal composition, is one prospective method for identifying people with an unknown DSD (31,32). Regardless of whether the genitalia appears unclear, a male-looking individual with bilateral undescended testes or a unilateral undescended testis and hypospadias must be evaluated for karyotype to rule out DSDs. Genetic testing using karyotyping revealed that 20 (50%) patients had the XY genotype, 19 (47.5%) patients had the XX genotype, and 1 (2.5%) patient had the XO genotype, which is indicative of Turner Syndrome. A chromosomal disorder called Turner syndrome influences female development. When most or all of an X chromosome is lacking from the cells in a girl's body, she develops Turner syndrome. Typically, each parent contributes one X chromosome to a girl. The mistake that results in the omitted chromosome seems to occur when the egg or sperm is being formed (33,34).

The most typical cause of DSD is congenital adrenal hyperplasia (CAH). CAH affects 1 in 15,000 people. The most frequent cause of CAH is a 21-hydroxylase deficiency, which causes a child to become virilized with 46, XX. Rapid diagnosis of the underlying cause of DSD is crucial because salt-wasting nephropathy affects 75% of people with 21-hydroxylase deficiency (35). All of the preliminary studies using the first-line tests, such as measuring 17-hydroxyprogesterone, blood electrolytes, determining AMF and gonadotrophin levels, cytogenetic analysis (karyotype), and an abdominal ultrasound to look for müllerian structures, culminating in the final diagnosis, that indicates that the majority of the participants were detected with CAH (55%), accompanied by 37.5% with Testicular Feminization Syndrome, and the remaining with rare types that were left un-concluded. Our study results are consistent with Aboud and Khadim (2014) where CAH was the most common disorder in 46, XX DSD, Mullerian structures generally indicate a genetic male sex or gonadal dysgenesis in a genetic male with insufficient anti-Mullerian hormone production (AMH) (22,36,37). A rare hereditary type of male pseudo-hermaphroditism known as androgen insensitivity (testicular feminisation) syndrome affects biologically normal women with proper breast development, normal external genitalia, a vagina of varying depth, no uterus, and thin or no pubic and axillary hair.

In some patients with DSD, laparoscopy is a useful diagnostic tool. It enables the visualisation and biopsy of the gonadal tissue in addition to a thorough examination of Müllerian derivatives (38). Additional diagnostic laparoscopy on 31 of the 40 (77.5%) patients found that 30% of the patients had small uteri and ovaries, then 25% had intra-abdominal testis, and the remaining had both testis and ovaries as well as TFS.

The study has certain limitations that include small population size, to generalise the findings. Similarly, the DSDs association with other biological, or socio-economic determinants has not been established in the study. Iraq is a conservative society, therefore convincing parents to such studies is difficult. This is one of the reasons, why our study sample is low. However, our study found the incidence of DSD in Duhok city, that can be further extrapolated to other cities and multi-centres for more generalisation of the data.

All the studies will help in a better understanding and management of DSD. By addressing issues with anatomy, fertility, gender identity, physical and psychosocial development, as well as other issues with physical, sexual, and mental health, management ultimately aims to maximise the long-term quality of life. The best way to do this is for the team to constantly and openly communicate with the patients and their families.

The current study is a small representative of the DSDs present in the Iraqi population. There is a paucity of research regarding the DSD incidence rate, prevalence rate, risk factors, and current status in the Iraqi population. While, the study found a higher proportion of ambiguous gender, and CAH to be the most common DSDs in the target population, future studies should focus more on the statistical analysis of the data. Laparoscopy is an established protocol to diagnose DSDs, but advanced karyotyping and other molecular studies are warranted to further explore the aetiology of the DSDs identified. Future studies should focus on methodological rigour and larger sample size to elucidate the incidence and prevalence of DSD in the Iraqi population.

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Conflict of interest

The authors declare that they have no competing interests.

References

1. Hiort O, Birnbaum W, Marshall L, Wünsch L, Werner R, Schröder T, et al. Management of disorders of sex development. Nat Rev Endocrinol 2014;10:520-9.
2. Dearden L, Bouret SG, Ozanne SE. Sex and gender differences in developmental programming of metabolism. Mol Metab 2018;15:8-19.
3. Witchel SF. Disorders of sex development. Best Pract Res Clin Obstet Gynaecol. 2018;48:90-102.
4. Polipalli SK, Karra VK, Jindal A, Puppala M, Singh P, Rawat K, et al. Cytogenetic Analysis for Suspected Chromosomal Abnormalities; A Five Years Experience. J Clin Diagn Res. 2016;10:GC01-5.
5. Chawla R, Rutter M, Green J, Weidler EM. Care of the adolescent patient with congenital adrenal hyperplasia: Special considerations, shared decision making, and transition. Semin Pediatr Surg. 2019;28:150845.
6. Fausto-Sterling A. Gender/Sex, Sexual Orientation, and Identity Are in the Body: How Did They Get There? J Sex Res. 2019;56:529-55.
7. Hughes IA. Disorders of sex development: a new definition and classification. Best Pract Res Clin Endocrinol Metab. 2008;22:119-34.
8. Lee PA, Nordenström A, Houk CP, Ahmed SF, Auchus R, Baratz A, et al. Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care. Horm Res Paediatr. 2016;85:158-80.
9. Byne W, Karasic DH, Coleman E, Eyler AE, Kidd JD, Meyer-Bahlburg HF, Pleak RR, Pula J. Gender dysphoria in adults: an overview and primer for psychiatrists. Transgender Health. 2018 Dec 1;3(1):57-A3.
10. García-Acero M, Moreno O, Suárez F, Rojas A. Disorders of sexual development: current status and progress in the diagnostic approach. Curr Urol. 2019;13(4):169-78.
11. Mattioli G, Lazzeroni P, Paraboschi I, Di Iorgi N, Napoli F, Maghnie M. Testis Development and Descent 8. Endocrinology of the Testis and Male Reproduction. 2017;1:273.
12. Kareem RA, Al-Faisal AH. Hormonal Disturbance in Ambiguous Patients. Iraqi J Biotechnol. 2019;18.
13. Mehmood KT, Rentea RM. Ambiguous Genitalia and Disorders of Sexual Differentiation. 2022 Aug 29. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.
14. Kremen J, Chan YM, Swartz JM. Recent findings on the genetics of disorders of sex development. Curr Opin Urol. 2017;27:1-6.
15. García-Acero M, Moreno O, Suárez F, Rojas A. Disorders of Sexual Development: Current Status and Progress in the Diagnostic Approach. Curr Urol. 2020;13:169-78.
16. Moshiri M, Chapman T, Fechner PY, Dubinsky TJ, Shnorhavorian M, Osman S, Bhargava P, Katz DS. Evaluation and management of disorders of sex development: multidisciplinary approach to a complex diagnosis. Radiographics. 2012 Oct;32(6):1599-618.
17. Schnitzer JJ, Donahoe PK. Surgical treatment of congenital adrenal hyperplasia. Endocrinol Metab Clin North Am. 2001 Mar;30(1):137-54.
18. Terribile M, Stizzo M, Manfredi C, Quattrone C, Bottone F, Giordano DR, et al. 46,XX Testicular Disorder of Sex Development (DSD): A Case Report and Systematic Review. Medicina (Kaunas). 2019;55:371.
19. Wisniewski AB, Batista RL, Costa EMF, Finlayson C, Sircili MHP, Dénes FT, et al. Management of 46,XY Differences/Disorders of Sex Development (DSD) Throughout Life. Endocr Rev. 2019;40:1547-72.
20. Sandberg DE, Gardner M, Kopec K, Urbanski M, Callens N, Keegan CE, et al. Development of a decision support tool in pediatric Differences/Disorders of Sex Development. Semin Pediatr Surg. 2019;28:150838.
21. Oliveira LR, Longui CA, Guaragna-Filho G, Costa JL, Lanaro R, Silva DA, et al. Androgens by immunoassay and mass spectrometry in children with 46, XY disorder of sex development. Endocr Connect. 2020;9:1085-94.
22. Walia R, Singla M, Vaiphei K, Kumar S, Bhansali A. Disorders of sex development: a study of 194 cases. Endocr Connect. 2018;7:364-71.
23. Tejwani R, Jiang R, Wolf S, Adkins DW, Young BJ, Alkazemi M, et al. Contemporary Demographic, Treatment, and Geographic Distribution Patterns for Disorders of Sex Development. Clin Pediatr (Phila). 2018;57:311-8.
24. Mazen I, Hiort O, Bassiouny R, El Gammal M. Differential diagnosis of disorders of sex development in Egypt. Horm Res. 2008;70:118-23.
25. Ellaithi M, Kamel A, Saber O. Consanguinity and disorders of sexual developments in the Sudan. Sudan J Med Sci. 2011;6.
26. Al-Jurayyan NA. Ambiguous genitalia: two decades of experience. Ann Saudi Med. 2011;31:284-8.
27. Bashamboo A, McElreavey K. Consanguinity and disorders of sex development. Hum Hered. 2014;77:108-17.
28. Abokifa AM, El Badawy RI, Anwar HW, El Sagheer YE. Disorders of sexual development in proximal hypospadias in children. Egypt J Hosp Med. 2019;77:5771-5.
29. Arap S, Mitre AI. Penoscrotal hypospadias. Braz J Urol. 2000;26:304-14.
30. Kaefer M, Rink RC. Treatment of the Enlarged Clitoris. Front Pediatr. 2017;5:125.
31. Ahmed SF, Alimusina M, Batista RL, Domenice S, Lisboa Gomes N, McGowan R, et al. The Use of Genetics for Reaching a Diagnosis in XY DSD. Sex Dev. 2022;16:207-24.
32. Pang KC, Feldman D, Oertel R, Telfer M. Molecular Karyotyping in Children and Adolescents with Gender Dysphoria. Transgend Health. 2018;3:147-53.
33. Sybert VP, McCauley E. Turner's syndrome. N Engl J Med. 2004;351:1227-38.
34. Viuff M, Skakkebaek A, Nielsen MM, Chang S, Gravholt CH. Epigenetics and genomics in Turner syndrome. Am J Med Genet C Semin Med Genet. 2019;181:68-75.
35. Tschaidse L, Quinkler M, Claahsen-van der Grinten H, Nordenström A, De Brac de la Perriere A, Auer MK, et al. Body Image and Quality of Life in Women with Congenital Adrenal Hyperplasia. J Clin Med. 2022;11:4506.
36. Kadhim MM, Aboud MJ. Disorders of Sex Development: Molecular Versus Clinical and Cytogenic Studies and Their Correlation with Diagnostic Outcome and Sex of Rearing in A Local Community. J Med Sci Clin Res. 2014;2:1626-46.
37. Khuder HA. Androgen Hormone and Male Infertility. Int J Res Appl Sci Biotechnol. 2021;8:168-74.
38. Moriya K, Morita K, Mitsui T, Kitta T, Nakamura M, Kon M, et al. Impact of laparoscopy for diagnosis and treatment in patients with disorders of sex development. J Pediatr Urol. 2014;10:955-61.